

Rheological Behaviour of Saturated Polyglycolysed Glycerides

E. BOURRET*, V. RATSIMBAZAFY, L. MAURY* AND C. BROSSARD

Laboratory of Pharmaceutical Technology, Faculty of Pharmacy, 87025 Limoges, and *Laboratory of Molecular and Structural Physics, Faculty of Pharmacy, 34060 Montpellier, France

Abstract—Seven saturated polyglycolysed glycerides (Gelucires) of melting points varying from 42 to 53°C and hydrophilic-lipophilic balance values from 2 to 14 were selected. Their rheological behaviour was determined by adjustment of the flow curves to the Ostwald power-law and by statistical assessment of the flow index. The flow of Gelucires was slightly shear thickening. This shear thickening rose when the temperature and the lipophilic specificity of the Gelucire increased. This behaviour accounted for a reorganization of the particles under the shear which became easier when the temperature increased and when the degree of condensation of the polyethylene glycol chains decreased with lipophilicity of the Gelucires.

Preparation of extended-release solid dosage forms requires the use of special excipients such as saturated polyglycolysed glycerides (Gelucires). Each Gelucire is characterized by its melting point and its hydrophilic-lipophilic balance (HLB). The choice of the appropriate Gelucire according to its melting point and its HLB value allows modulation of the kinetics and rate of drug release (Kopcha et al 1990; Prapaitrakul et al 1991; Ratsimbazafy & Brossard 1991). These amphiphilic excipients are waxy bases essentially used to formulate semi-solid matrices. After fusion of waxes, the drugs are dissolved or dispersed in Gelucires kept at a temperature higher than its melting point. Then the melted mixtures are cast in hard gelatin capsules. Consequently, it seemed interesting to examine the consistency and the viscosimetric properties of these melted lipidic compounds before associating them with drugs.

Recently, Duclos et al (1993) noted a dilatant behaviour for Gelucires used alone. Such a behaviour had also been observed by Chemtob & Zuber (1977) for glyceryl stearate and by Fabregas (1991) and Margarit et al (1992) for suppository excipients, that is to say, fatty substances similar to low HLB Gelucires and sometimes used to prepare semi-solid matrix capsules (Naidoo 1989).

The aim of this work was to study the rheological behaviour of several Gelucires, first as a function of their HLB, then in terms of temperature.

Materials and Methods

Gelucires

Seven Gelucires (Gattefossé, France) of increasing HLB were selected: 50/02, 46/07, 48/09, 53/10, 42/12, 50/13 and 44/14, where the first figure corresponds to the melting point in °C and the second to the HLB value.

Rheological behaviour

Rheological behaviour and apparent viscosities were determined on a coaxial cylinder viscosimeter (Rheomat 15 T

Contraves) fitted with the thermostated measuring system MS-A. Fifteen shear rates varying from 11 to 702 s⁻¹ were applied sequentially on the same sample for 15 s.

Shear rate measurements were made in replicate in the case of the first two Gelucires and then as a single value for the other Gelucires.

Rheological measurements were performed 30°C above the melting point. The temperature influence was studied on the same sample with Gelucires 50/02 and 50/13 at 50, 60, 70, 80 and 90°C.

Analysis of results

Rheograms were fitted to the Ostwald equation:

$$\tau = k\dot{\gamma}^n \quad (1)$$

where $\dot{\gamma}$ is the shear rate applied to the sample, τ is the shear stress, and k and n are the characteristics of the rheological behaviour (k = consistency index, n = flow index).

The flow index is equal to unity if the flow is newtonian. A value statistically either greater or smaller than unity shows respectively a shear thickening or a shear thinning.

This index was determined by linear regression according to the logarithmic form of equation 1:

$$\ln \tau = \ln k + n \ln \dot{\gamma} \quad (2)$$

$$\text{or} \quad \ln \tau = f(\ln \dot{\gamma}) \quad (3)$$

Thus, the flow index is the slope of the obtained least-square line. A linearity statistical test was used to calculate the deviations of the regression and to show the model validity. The divergence to the newtonian flow was tested statistically by comparison with the unity value of the linear regression coefficient n .

When the results were consistent with newtonian flow, the values of the consistency index, k , were compared with the average newtonian viscosity index which was calculated with viscosity indexes obtained at the different shear rates.

Results and Discussion

Influence of HLB on flow and viscosity curves

Flow and viscosity curves (Figs 1, 2) at 30°C above the

Correspondence: C. Brossard, Laboratory of Pharmaceutical Technology, Faculty of Pharmacy, 87025 Limoges, France.

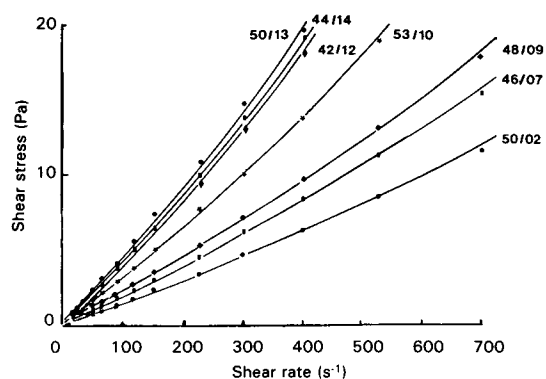


FIG. 1. Flow curves of Gelucires obtained 30°C above their melting points.

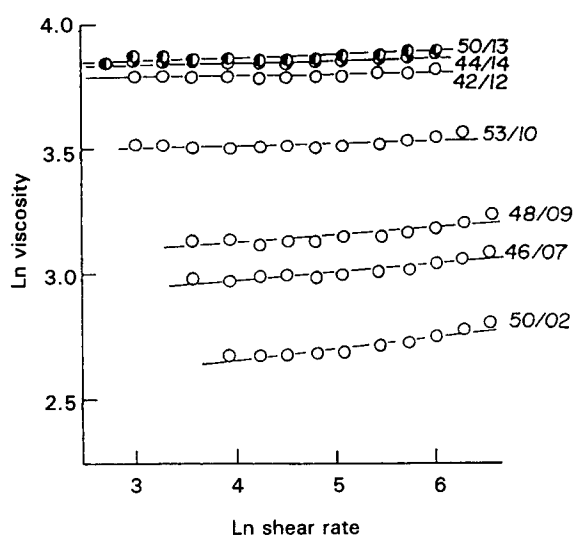


FIG. 2. Viscosity curves of Gelucires.

melting point of each Gelucire show that, whatever the shear rate, shear stress and apparent viscosity increase with HLB. Simultaneously, for all Gelucires, $\tau = f(\dot{\gamma})$ rheograms show a small concavity which indicates a slight increase in viscosity at increasing shear rate (Fig. 1). This increase is visible on the viscosity curves with logarithmic scales (Fig. 2). It always remains with a weak amplitude and it is clear when the HLB value decreases from 14 to 2.

Influence of Gelucire HLB on flow indexes

To verify whether the increase of the viscosity really means a shear thickening, a linear model adjustment according to $\ln \tau = \ln k + n \ln \dot{\gamma}$ was investigated. The linearity test is always highly significant of a good fitting. In all the fittings which gave rise to the flow index estimate, the variance, r^2 , which indicated the proportion of the shear stress explained by the shear rate was always equal to 0.999.

The regression coefficient values, n , which give the flow indexes (Table 1) are scarcely greater than 1 and do not directly allow a conclusion on the flow behaviour. The comparison of these values with the theoretical value of 1 by a Student's t -test will, however, show if there is a significant

Table 1. Flow index \pm 95% confidence interval and significant degree of its comparison with unity by a Student's t -test: influence of Gelucire at mp + 30°C.

Gelucire	$n \pm 95\%$ confidence interval
50/02	$1.047 \pm 0.013^{***}$
46/07	$1.034 \pm 0.010^{***}$
48/09	$1.030 \pm 0.013^{***}$
53/10	$1.011 \pm 0.009^*$
42/12	$1.007 \pm 0.006^*$
50/13	$1.007 \pm 0.004^{**}$
44/14	$1.007 \pm 0.006^*$

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

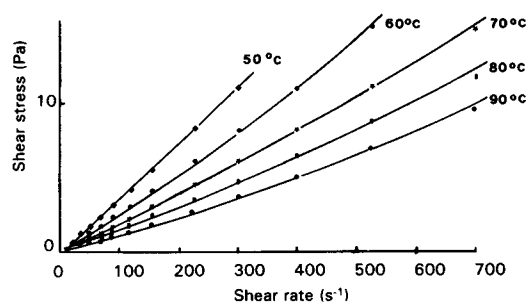


FIG. 3. Influence of temperature on flow curves of Gelucire 50/02.

shear thickening; the lower the probability, the more the difference with unity is important and the more the value expresses the shear thickening.

Test results (Table 1) show that the difference between experimental values n and 1 is always widely significant for a non-newtonian flow because the significant probability level is always less than 0.05. However, this probability is less than 0.001 for the first three Gelucires, which means a clear shear thickening. For the following Gelucires which have an HLB value greater than 10, the significance of the differences is less since the P values are greater. The shear thickening is then very weak and the influence of the HLB on the flow indexes is not so clear: for these Gelucires, the HLB values are close together (10 to 14, rather than 2 to 10 for the first group of Gelucires). Fig. 2 exhibits quite clearly these two groups of Gelucires.

To corroborate these results, the variations unexplained by the linear model—residual variations—were used as an estimate of the experimental error. This allowed the assessment of the 0.95 confidence limits of regression coefficients. These intervals illustrate the divergence to unity, the latter lessening with the increase in HLB (Table 1).

Influence of temperature

The influence of temperature on the shear thickening was examined with two Gelucires of the same melting point, one high HLB and one low HLB.

For Gelucire 50/02, at the temperatures of 60, 70, 80 and 90°C, the same concavity of the rheograms and the same increase in the viscosity under the shear effect can be observed (Figs 3, 4). Regression coefficients (Table 2) of the Ostwald bilogarithmic line $\ln \tau = f(\ln \dot{\gamma})$ are significantly different from unity for these temperatures; the significant

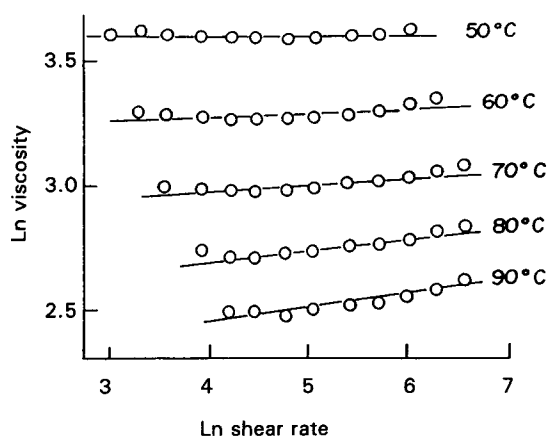


FIG. 4. Viscosity curves of Gelucire 50/02 at different temperatures.

Table 2. Flow index \pm 95% confidence interval and significant degree of its comparison with unity by a Student's *t*-test: influence of temperature with Gelucire 50/02.

Temperature (°C)	$n \pm 95\%$ confidence interval
90	$1.054 \pm 0.018^{***}$
80	$1.042 \pm 0.015^{***}$
70	$1.028 \pm 0.013^{***}$
60	$1.016 \pm 0.015^*$
50	0.999 ± 0.009

* $P < 0.05$, *** $P < 0.001$.

probability level of the difference increases when temperature falls from 90 to 60°C, the difference from unity being reduced with temperature. At 50°C, the rheogram $\tau = f(\dot{\gamma})$ is clearly linear and the regression coefficient is not statistically different from unity. The 95% confidence limits of the slope of the regression line match these observations. These rheograms, the viscosity curves and the flow index n values reveal that shear thickening appears when the temperature rises above the melting point.

For Gelucire 50/13, at the temperatures of 60, 70, 80 and 90°C, the comparison tests against unity of the regression coefficients according to the relationship $\ln \tau = f(\ln \dot{\gamma})$ do not indicate significant shear thickening. The confidence intervals show well that the flow is typically newtonian (Table 3). At 50°C, Gelucire 50/13 is not completely melted unlike Gelucire 50/02, and further comparisons are not possible.

The adjustment to the power law gives the assessment of the index k which must be equal to the newtonian viscosity index when the flow is shown to be newtonian. Also, in this case, the average of the viscosity was calculated from the measurements at different shear rates (10–12 measurements according to the temperature). This average is affected by its 0.95 confidence limits and must be compared with the value of the index k . These two values are similar (Table 3), confirming the newtonian behaviour at these temperatures.

It should be noted that the rheograms were obtained with the same sample successively taken from 50 to 60, 70, 80 and 90°C. In the case of Gelucire 50/02, the product exhibiting the greatest shear thickening, time factor and past history of the previously sheared material do not affect subsequent results and similar flow indexes at 80°C are obtained (Tables 1, 2). For Gelucire 50/13, however, rheological behaviour and flow indexes at 80°C are different because the operating procedure has a greater influence as Gelucire has a very weak shear thickening behaviour. Although the study on the influence of temperature reveals a newtonian behaviour of Gelucire 50/13, when rheological measurements are carried out successively at different temperatures on the same sample, the actual behaviour of Gelucire 50/13 is weakly shear thickening, as the measurements carried out on fresh samples show (Table 1).

Figs 3 and 4 show that apparent viscosities of Gelucires decrease when the temperature rises. This decrease is exponential and follows an Arrhenius relationship:

$$\eta = A e^{B/T} \quad (4)$$

where η is apparent viscosity, T is absolute temperature (K), and A and B are constants.

Fig. 5 illustrates the logarithmic form of equation 4:

$$\ln \eta = \ln A + \frac{B}{T} \quad (5)$$

Gelucire 50/02 measured at the shear rate of 118 s^{-1} .

This work demonstrates a slight shear thickening of Gelucires, depending on the HLB value and the temperature, being more for $\text{HLB} < 10$ at higher temperatures.

The choice of Gelucires 50/02 and 50/13, with the same melting point but very different HLB values, allows us to link their flow differences to their composition. Gelucires of low HLB contain no or little polyethylene glycol (PEG) whereas Gelucires of high HLB include PEG esters with a high degree of condensation (Waginaire & Glas 1981).

When shearing stops, immediate return to zero point occurs. The slight shear thickening observed in the rising part of the rheogram, depending on the initial structure, usually stems from a reorganization; in media where particles in

Table 3. Influence of temperature with Gelucire 50/13: flow index \pm 95% confidence interval, consistency indexes and newtonian viscosity index (Pa s) \pm 95% confidence interval. A Student's *t*-test showed no significant differences from unity for flow indexes.

Temperature (°C)	$n \pm 95\%$ confidence interval	Consistency index	Newtonian viscosity
90	0.990 ± 0.02	0.039	0.0381 ± 0.0008
80	0.980 ± 0.03	0.053	0.0490 ± 0.0002
70	0.993 ± 0.008	0.066	0.0649 ± 0.0006
60	0.990 ± 0.01	0.093	0.0922 ± 0.0009

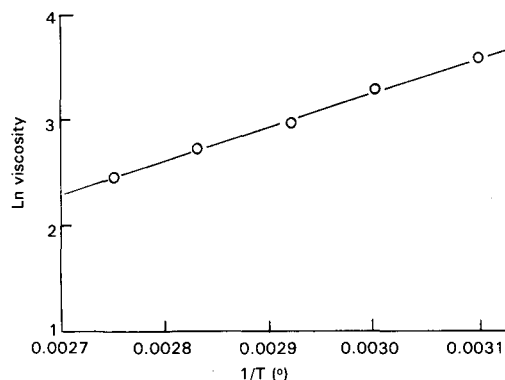


FIG. 5. Arrhenius plot of temperature influence on apparent viscosity of Gelucire 50/02 at shear rate $\dot{\gamma} = 118 \text{ s}^{-1}$.

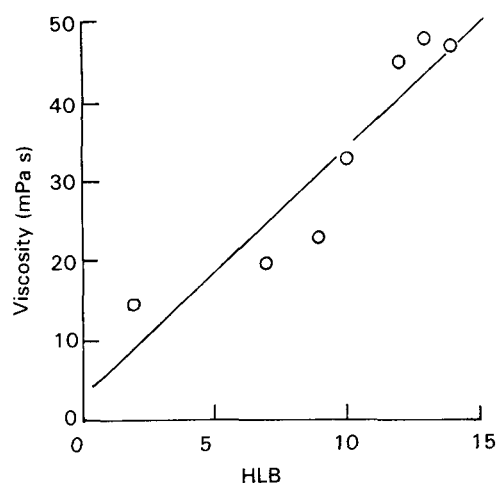


FIG. 6. Influence of Gelucire HLB on apparent viscosity at shear rate $\dot{\gamma} = 118 \text{ s}^{-1}$.

suspension are free of strong bond, there would be local rearrangement of particles, due to shear effect, which would show through a slight increase in viscosity (Burlage et al 1963; Bourret et al 1988). The observations collected here may effectively account for such a reorganization; a structural rearrangement is possible when the degree of PEG condensation is low but becomes difficult when the poly-

ethylene chain is extended. This reorganization is made easier by the acceleration of Brownian motion under the effect of temperature. The nearer to melting point the temperature is, the lower the degree of chain mobility and the less shear thickening. When shear rate returns to zero, initial structure is restored.

The increase of the shear stress and that of the Gelucire apparent viscosity (Fig. 6) with the hydrophilic specificity may also be explained by their compositions. With a steric hindrance of PEG chains in high HLB Gelucires, the chain lengthening induces an increase of the friction forces and then a resistance to flow.

Acknowledgements

The authors are grateful to the Gattefossé Corporation for their gift of the Gelucires.

References

- Bourret, E., Rueda Rodriguez, C., Fortuné, R., Bardet, L. (1988) Comportement rhéologique des sols d'acide polysilicique-I-Influence des facteurs pH, concentration, temps. *Rheo. Acta* 27: 52-60
- Burlage, H. M., Lee, C., Rising, L. W. (1963) *Physical and Technical Pharmacy*. McGraw-Hill Book Company, New York, pp 477-492
- Chemtob, C., Zuber, M. (1977) Etude des stéarates de glycols et de glycérol de la Pharmacopée Française. Incidence de leurs propriétés sur la formulation des émulsions. *Proc. Congr. Int. Technol. Pharm.* 1, 3: 9-21
- Duclos, R., Saiter, J. M., Ratsimbazafy, V., Brossard, C. (1993) Viscosity, release and D.S.C. studies of lipid matrix capsules containing derivatives of theophylline. *Proc. Pharm. Technol. Conf.* 12, 1: 500-509
- Fabregas, J. L. (1991) Softening of semi-synthetic suppository bases. *Drug Dev. Ind. Pharm.* 17: 1083-1096
- Kopcha, M., Tojo, K.J., Lordi, N.G. (1990) Evaluation of methodology for assessing release characteristics of thermosoftening vehicles. *J. Pharm. Pharmacol.* 42: 745-751
- Margarit, M. V., Rodriguez, I. C., Cerezo, A. (1992) Rheological study of rectal formulations of sodium valproate. *Drug Dev. Ind. Pharm.* 18: 79-92
- Naidoo, N. T. (1989) Encapsulation and in vitro release of indomethacin from semi-solid matrix capsules. *Int. J. Pharm.* 55: 53-57
- Prapaitrakul, W., Sprockel, O. L., Shivanand, P. (1991) Release of chlorpheniramine maleate from fatty acid ester matrix disks prepared by melt-extrusion. *J. Pharm. Pharmacol.* 43: 377-381
- Ratsimbazafy, V., Brossard, C. (1991) Les Gélucire et le ralentissement de la libération des principes actifs. *STP Pharma Prat.* 1: 335-349
- Wagnaire, L., Glas, B. (1981) Gélucire. *Bull. Tech. Gattefossé* 74: 7-12